PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing (*day/month/year*) 22 FEB 2007
Applicant's or agent's file reference 2848-79-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US06/09078	13 March 2006 (13.03.2006)	11 March 2005 (11.03.2005)

International Patent Classification (IPC) or both national classification and IPC

IPC(8): **A61K 31/435**(2006.01)
USPC: 514/277

Applicant

THE REGENTS OF THE UNIVERSITY OF COLORADO

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	11 January 2007 (11.01.2007)	James B. Anderson Telephone No. 571-272-9038
Facsimile No. (571) 273-3201		

Form PCT/ISA/237 (cover sheet) (April 2005)

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-35	YES
	Claims NONE	NO
Inventive step (IS)	Claims 21-35	YES
	Claims 1-20	NO
Industrial applicability (IA)	Claims 1-35	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claim 3 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 3 is indefinite for the following reason(s): it is not clear what is intended by the term "substantial portion". For example, is it applicant's intent that 51% is a "substantial portion"?

Claim 6 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 6 is indefinite for the following reason(s): it is not clear what is intended by the phrase "substantially the same time period".

Claim 8 is objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claim is not fully supported by the description. The application, as originally filed, did not describe the HDAC inhibitors encompassed by the claim in sufficient detail so as to demonstrate possession of the claimed invention. Only those HDAC inhibitors explicitly named in the disclosure are supported by the description (*e.g.* those inhibitors recited in claims 9-12).

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 21-35 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the treatment of EGFR-resistant cancers with a combination of an EGFR inhibitor and an inhibitor of histone deacetylase. Although both EGFR inhibitors and histone deacetylase inhibitors are known in the art as treatments for cancer, the skilled artisan would not be motivated to treat an EGFR-resistant cancer with an inhibitor of EGFR. Further, the prior art does not teach or fairly suggest that histone deacetylase inhibitors would be effective in enhancing the effect of an EGFR inhibitor in EFGR-resistant cancers.

Claims 1-20 lack an inventive step under PCT Article 33(3) as being obvious over Baselga *et al.* (Journal of Clinical Oncology, 2002) in view of Monneret (Eur. J. of Med. Chem., 2005). The instant claims are drawn to the treatment of cancer comprising administering a combination of an EGFR inhibitor and a histone deacetylase inhibitor. The claims lack an inventive concept because both EGFR inhibitors and histone deacetylase inhibitors are known in the art as agents useful in the treatment of cancer. For example, Baselga et al. discuss the efficacy of ZD1839 [gefitinib; Iressa], a selective oral EGFR inhibitor, in the treatment of five different tumor types (Abstract). Gefitinib was administered at doses ranging from 150 to 1000 mg/day). Similarly, Monneret discloses that inhibition of histone deacetylase represent a new strategy in the treatment of cancer (Abstract). The article reviews current clinical trials wherein histone deacetylase inhibitors are used to treat cancer. For example, MS-275 has reached phase II clinical trials. In a phase I study, MS-275 was used to treat patients with refractory solid tumors and lymphomas (page 10). The drug was administered at doses ranging from 2 to 10 mg/m^2 (*id.*). The reference further discloses the other histone deacetylase inhibitors recited in the instant claims (pages 2-11). It would have been obvious to the skilled artisan to administer both an EGFR inhibitor and a histone deacetylase inhibitor to treat cancer as both types of inhibitor were known in the art to be anticancer agents. Combination chemotherapy is well known in the art. As such, the claims lack an inventive concept because the skilled artisan would have been highly motivated to co administer two known anticancer agents.

Claims 1-20 lack an inventive step under PCT Article 33(3) as being obvious over Stefanie et al. (US 2005/0043233 A1; Published Feb. 24, 2005). The instant claims are drawn to the treatment of cancer comprising administering a combination of an EGFR inhibitor and a histone deacetylase inhibitor. The claims lack an inventive concept because both EGFR inhibitors and histone deacetylase inhibitors are known in the art as agents useful in the treatment of cancer. Stefanie et al. relates to a pharmaceutical combination comprising co-administration of active compounds for the treatment of diseases involving cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis (Abstract). Specifically, the reference relates to methods of treatment comprising administering a protein kinase inhibitor and at least one further chemotherapeutic agent (page 1, ¶ [0002]-[0012]). EGFR inhibitors are explicitly disclosed at page 2, ¶ [0050]-[0051] and page 9, ¶ [0159]. The additional chemotherapeutic agent used in combination with the protein kinase inhibitor includes

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Supplemental Box
In case the space in any of the preceding boxes is **not sufficient.**

histone deacetylase inhibitors such as SAHA, MD-275, valproic acid, trichostain A, CBHA and LAQ824 (page 14, ¶ [0218]. Diseases to be treated include malignant neoplasias or cancers, including lung cancer and epithelial cancers (pages 4-5, ¶ 0078]. Doses and administration regimens are disclosed at pages 15-16, ¶¶ [0225]-[0234]. It would have been obvious to the skilled artisan to administer both an EGFR inhibitor and a histone deacetylase inhibitor to treat cancer as both types of inhibitor were known in the art to be anticancer agents and Stefanic et al. suggest using combined chemotherapy to treat cancer. As such, the claims lack an inventive concept because the skilled artisan would have been highly motivated to co administer an EGFR inhibitor and an inhibitor of histone deacetylase.

Claims 1-35 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.